META-ANALYSIS

Predicting Fluid Responsiveness Using Carotid Ultrasound in Mechanically Ventilated Patients: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies

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BACKGROUND: A noninvasive and accurate method of determining fluid responsiveness in ventilated patients would help to mitigate unnecessary fluid administration. Although carotid ultrasound has been previously studied for this purpose, several studies have recently been published. We performed an updated systematic review and meta-analysis to evaluate the accuracy of carotid ultrasound as a tool to predict fluid responsiveness in ventilated patients.

METHODS: Studies eligible for review investigated the accuracy of carotid ultrasound parameters in predicting fluid responsiveness in ventilated patients, using sensitivity and specificity as markers of diagnostic accuracy (International Prospective Register of Systematic Reviews [PROSPERO] CRD42022380284). All included studies had to use an independent method of determining cardiac output and exclude spontaneously ventilated patients. Six bibliographic databases and 2 trial registries were searched. Medline, Embase, Emcare, APA PsycInfo, CINAHL, and the Cochrane Library were searched on November 4, 2022. Clinicaltrials.gov and Australian New Zealand Clinical Trials Registry were searched on February 24, 2023. Results were pooled, meta-analysis was conducted where possible, and hierarchical summary receiver operating characteristic models were used to compare carotid ultrasound parameters. Bias and evidence quality were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.

RESULTS: Thirteen prospective clinical studies were included (n = 648 patients), representing 677 deliveries of volume expansion, with 378 episodes of fluid responsiveness (58.3%). A meta-analysis of change in carotid Doppler peak velocity (ΔCDPV) yielded a sensitivity of 0.79 (95% confidence interval [CI], 0.74–0.84) and a specificity of 0.85 (95% CI, 0.76–0.90). Risk of bias relating to recruitment methodology, the independence of index testing to reference standards and exclusionary clinical criteria were evaluated. Overall quality of evidence was low. Study design heterogeneity, including a lack of clear parameter cutoffs, limited the generalizability of our results.

CONCLUSIONS: In this meta-analysis, we found that existing literature supports the ability of carotid ultrasound to predict fluid responsiveness in mechanically ventilated adults. ΔCDPV may be an accurate carotid parameter in certain contexts. Further high-quality studies with more homogenous designs are needed to further validate this technology. (Anesth Analg 2024;138:1174–86)

KEY POINTS

- **Question:** Can carotid ultrasound accurately predict fluid responsiveness in mechanically ventilated patients?
- **Findings:** Change in carotid Doppler peak velocity demonstrates moderate accuracy in predicting fluid responsiveness in ventilated patients.
- **Meaning:** Existing literature is supportive of carotid ultrasound for prediction of fluid responsiveness although study heterogeneity and undefined diagnostic cutoffs limit definitive conclusions.

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Accurate evaluation of fluid status in intubated, critically ill patients is important for patient management, as both hypovolemia and fluid overload can have deleterious consequences.[1–14] For this reason, assessment of fluid responsiveness has become central to decision-making. Fluid-responsive (FR) patients, also known as "fluid responders," are those who respond to volume administration with an increase in stroke volume. In such patients, both ventricles are assumed to be operating on the ascending portion of the Frank-Starling curve.[15] Current literature suggests that indices previously heralded as highly predictive such as pulse pressure variation (PPV) may not be as reliable outside the highly controlled environment and narrow patient cohort in which they were originally studied.[16,17] When coupled with observations that only 50% of critically ill patients are FR,[18,19] these data suggest that accurate methods of predicting fluid responsiveness are still needed.

Among the numerous techniques proposed to predict fluid responsiveness,[20–25] carotid ultrasound is the most novel technique.[26,27] It is noninvasive, requires only a small probe footprint, is less technically challenging than assessment of left ventricular (LV) outflow tract flow,[28] and has demonstrated acceptable intra- and interobserver agreement.[26,29,30] Drawbacks to carotid ultrasound for volume assessment include surgery to the region, pathology of the carotid vessel such as high-grade stenosis, arrhythmias, and impairment of cerebral autoregulation.[31–33]

Unfortunately, study heterogeneity has limited the generalizability and applicability of carotid ultrasound to critically ill patients. Most reviews and meta-analyses have analyzed both mechanically ventilated and spontaneously breathing patients.[34–37] As cardiovascular mechanics may differ between spontaneously breathing and positive pressure ventilated patients,[38] this mixing of patient cohorts likely confounds results and limits applicability.[34–37] The single systematic review and meta-analysis investigating solely mechanically ventilated adult patients is itself limited by a low number of included studies.[39] Since the 2018 publication of this review, 8 more relevant studies[40–47] have been performed.

To update the existing literature to include these recent studies, we performed a systematic review to pool all relevant literature regarding the accuracy of carotid ultrasound in predicting fluid responsiveness in ventilated patients. Where possible, we performed meta-analysis to determine the accuracy of this method.

METHODS

This study was conducted in line with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines for study protocols.[48] Conducting and reporting of this systematic review was done in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines[49] (Supplemental Digital Content 1, PRISMA-DTA Checklist, http://links.lww.com/AA/E629). Methodology for this review was predesigned and registered with the International Prospective Register of Systematic Reviews (PROSPERO number CRD42022380284).

Study Characteristics

Participants and Setting. Eligible studies examined patients over 18 years of age who were mechanically ventilated. These patients were either admitted to an intensive care unit (ICU), undergoing anesthesia in an operating theater (OT), or both. Studies on pediatric patients and healthy volunteers were excluded to allow generalizability of results to the ventilated adult population. To avoid confounding due to noncritically ill subjects, spontaneously breathing patients, healthy volunteers, or children, we excluded studies of nonmechanically ventilated patients, intubated patients spontaneously breathing, healthy volunteers or children.

Index Tests and Reference Standards. Index tests were any carotid ultrasound parameters. Reference standards were any independent means of measuring change in cardiac output or equivalent, that is, cardiac index, stroke volume, stroke volume index. Studies that examined carotid ultrasound parameters but did not have an independent means of measuring change to cardiac output were excluded.

Target Condition. The target condition was fluid responsiveness, as defined by each individual study. Studies that did not include the assessment of fluid responsiveness were excluded, as determining diagnostic accuracy of index tests in predicting fluid responsiveness would not have been possible. The principal diagnostic accuracy measures were sensitivity and specificity.

Study Design and Report Characteristics. This review included only prospectively performed studies. Studies published in languages other than English were excluded from database and registry searches. Relevant studies in languages other than English were identified through review of selected studies bibliographies. These studies were translated to English via the Google Translate function. If the translation was inadequate for accurate data extraction, these studies were excluded.

Information Sources

Publications were identified through searches of 6 bibliographic databases and 2 trial registries. Ovid

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MEDLINE(R) ALL 1946 to November 2, 2022, Embase 1974 to 2022 November 2 (Ovid), Ovid Emcare 1995 to 2022 week 43, APA PsycInfo 1806 to October week 4 2022 (Ovid), CINAHL (EBSCOhost), and Cochrane Library (Wiley) were searched on November 4, 2022. Clinicaltrials.gov and Australia New Zealand Clinical Trials Registry (ANZCTR) were searched on 24 February 2023. Bibliographies of included studies were examined for additional publications.

Search Strategy

Search strategies were developed by a medical librarian (H.W.) in consultation with a topic expert (S.W.). Potential search terms were identified through text mining in PubMed PubReMiner[50] using the query "ultrasonography AND carotid AND fluid." Search terms retrieved through text mining were extensively tested for usefulness and relevance in Ovid Medline to develop the final search strategy. A "gold set" of 10 relevant publications identified by a topic expert (S.W.) during scoping searches were also checked for further search terms and used to validate search strategies (Supplemental Digital Content 1, Search Strategy, http://links.lww.com/AA/E629).

Final search strategies combined the general concepts of Ultrasonography AND Carotid Velocity-Time Integral AND Fluid Responsiveness using a combination of subject headings and text words. Search strategies were intentionally not limited to patient group to ensure that relevant records were not missed. Searches were limited to English language publications, and no date limits were applied. Animal studies, pediatric studies, book sections, comments, dissertations, and letters were removed from the search process where possible.

An initial search was developed for Ovid Medline (Figure 1) and then adapted for other databases adjusting subject headings and syntax as appropriate (Supplemental Digital Content 1, Database Searches, http://links.lww.com/AA/E629). Search syntax used in the Ovid databases was adapted for CINAHL (EBSCOhost) and Cochrane (Wiley) using the Polyglot Search Translator.[51] Trial registries were searched using the strategy "Ultrasound AND Carotid AND fluid." Review of reference lists in included papers was used to further identify relevant studies.

Study Selection

Database search results were exported to EndNote bibliographic management software (Clarivate) and duplicates were removed by H.W. In accordance with the search criteria, records were screened on publication type by H.W. within EndNote, and the following publication types were excluded: book sections, comments, dissertations, and letters. All remaining records were loaded into Covidence systematic review software (Veritas Health Innovation Ltd) for removal of remaining duplicates and screening on title and abstract.

Two independent reviewers (A.L. and S.W.) screened studies for eligibility (Figure 2). Studies that met inclusion criteria based on title and abstract, or where inclusion was uncertain, were appraised via full-text review. Each full text was assessed in duplicate to ensure eligibility for inclusion. Reviewers were not blinded to study authors or institutions. The bibliographies of full-text articles were perused to identify further relevant studies (snowballing). In the event of disagreement regarding study eligibility, a third reviewer (H.A.) was consulted to make a binding determination.

Data Collection, Management, and Definitions

Covidence software (Veritas Health Innovation Ltd) was used to aid study selection and data extraction. Data collected from each study included (1) study characteristics, including author name/s, year of publication, location of study, carotid parameter (the index test), cardiac output (CO) measure (the reference standard), fluid responsiveness (the target condition) threshold, study design, patient setting, type of patients, inclusion and exclusion criteria, number of patients, tidal volume (TV), age, sex, number of fluid responders and method of assessing fluid responsiveness; and (2) diagnostics performance, including sensitivity, specificity, area under the receiver operating characteristic curve (AUROC), relevant 95% confidence intervals (95% confidence interval [CI]) and *P* values, optimum cutoffs, and true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values. The principal diagnostic accuracy measures were sensitivity and specificity. A TP was defined as a diagnosis of FR for the study-specific carotid parameter, confirmed by the reference standard. A TN was considered a diagnosis of not FR for the study-specific carotid parameter, confirmed by the reference standard. A FP was considered a diagnosis of FR for the carotid parameter that was not confirmed by the reference standard. A FN was considered a diagnosis of not FR for the carotid parameter that was not confirmed by the reference standard.[53]

Assessment of Bias and Evaluation of Evidence Quality

The revised Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was utilized to categorize each domain as low, high, or unclear risk of bias.[54] The quality of evidence used to determine the performance of index tests was conducted using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.[53,55] Assessment of study bias and quality of evidence, in addition to data extraction, were all undertaken by 2 reviewers independently (A.L. and

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Ovid MEDLINE(R) ALL 1946 to November 02, 2022

1. ultrasonography/ or echocardiography/ or echocardiography, doppler/ or echocardiography, doppler, color/ or echocardiography, doppler, pulsed/ or focused assessment with sonography for trauma/ or ultrasonography, doppler/ or ultrasonography, doppler, duplex/ or ultrasonography, doppler, color/ or ultrasonography, doppler, pulsed/
2. (ultraso* or echocardiog* or sonograph* or doppler).ti,ab,kw.
3. 1 or 2
4. exp Carotid Arteries/
5. (carotid or cvti).ti,ab,kw.
6. (velocity time integral* or vti).ti,ab,kw.
7. blood flow velocity/ or blood flow velocit*.ti,ab,kw.
8. Hemodynamics/ or (hemodynamic* or haemodynamic*).ti,kw.
9. 4 or 5 or 6 or 7 or 8
10. exp Fluid Therapy/
11. isotonic solutions/ or crystalloid solutions/ or ringer's lactate/ or saline solution/ or ringer's solution/
12. (fluid* or isotonic or crystalloid or ringer* or saline or hypodermoclysis or rehydrat*).ti,ab,kw.
13. leg rais*.ti,ab,kw.
14. 10 or 11 or 12 or 13
15. 3 and 9 and 14
16. exp animals/ not humans/
17. (animal* or rat or rats or rodent* or rabbit* or swine or dogs).ti.
18. ((paediatric* or pediatric* or child* or infant* or neonat* or fetus) not adult*).ti.
19. (comment or editorial or letter or news or practice guideline).pt.
20. 16 or 17 or 18 or 19
21. 15 not 20
22. limit 21 to english language

Figure 1. Ovid Medline search strategy.

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A.B.). Extraction tables were then compared to create consensus tables. Differences in extracted data were identified and source material was reexamined to correct any discrepancies.

Statistical Analysis

In instances where the TP, TN, FP, or FN values were not provided in published materials, these values were back-calculated using a 2-way contingency table analysis platform.[56] These calculated figures were rounded to the nearest integer. Two by two tables for each study were then assembled. An alpha value of 0.05 was used for hypothesis testing.

Meta-analysis was conducted in line with contemporary standards.[57] Side-by-side (twin) forest plots were constructed to allow examination of variability between studies. To further examine between-study heterogeneity we used a hierarchical summary receiver operating characteristic (HSROC) model[58] but only for carotid ultrasound parameters that were analyzed in ≥5 study cohorts. A bivariate random effects model[59] was used to pool sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR), as heterogeneity was anticipated based on the design features of published studies.[60] The contribution, if any, of a threshold effect was evaluated by the HSROC shape, coupled with a Spearman's coefficient (for which a value ≥0.6 suggests a threshold effect). Publication bias was assessed using Deek's funnel plot asymmetry test.[61] If the number of studies proved amenable, meta-regression was considered to investigate potential effects of covariates on observed heterogeneity.

Data were analyzed using Stata (version 17.0; StataCorp LLC) via modules MIDAS (meta-analysis of diagnostic accuracy studies),[62] METANDI (meta-analysis of diagnostic accuracy using hierarchical logistic regression),[63] and METADTA (meta-analysis and meta-regression of diagnostic test accuracy)[64] in addition to MetaDTA: Diagnostic Test Accuracy Meta-Analysis v2.01, a web-based software available at https://crsu.shinyapps.io/dta_ma/.[65,66]

RESULTS

Study Selection and Study Characteristics

Database and registry searches yielded 7536 records, of which 4108 were screened on title and abstract and 70 were selected for full-text review. Additionally,

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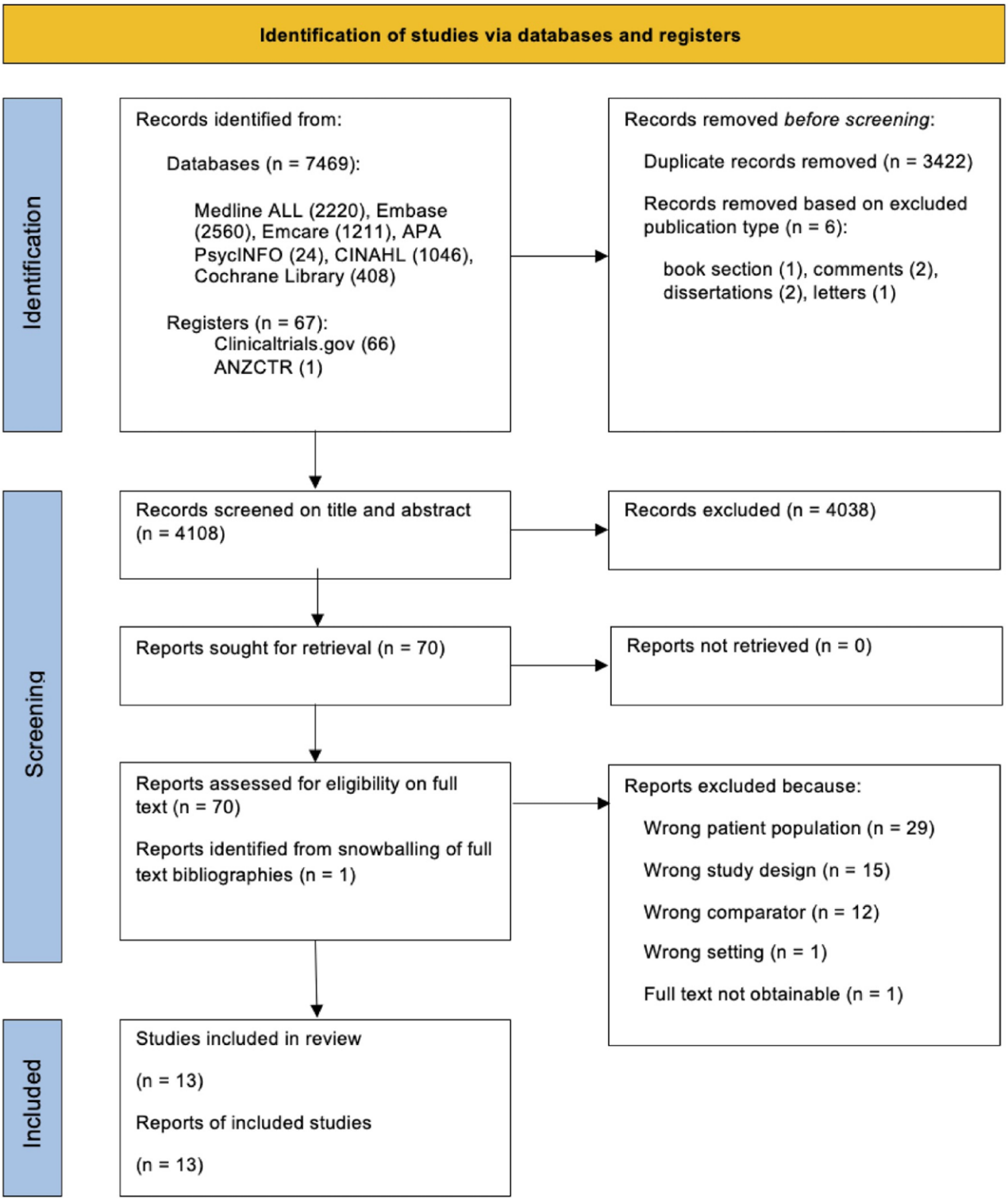
Identification of studies via databases and registers
Identification
Records identified from:
Databases (n = 7469):
Medline ALL (2220), Embase (2560), Emcare (1211), APA PsycINFO (24), CINAHL (1046), Cochrane Library (408)
Registers (n = 67):
Clinicaltrials.gov (66)
ANZCTR (1)
Records removed before screening:
Duplicate records removed (n = 3422)
Records removed based on excluded publication type (n = 6):
book section (1), comments (2), dissertations (2), letters (1)
Screening
Records screened on title and abstract (n = 4108)
Records excluded (n = 4038)
Reports sought for retrieval (n = 70)
Reports not retrieved (n = 0)
Reports assessed for eligibility on full text (n = 70)
Reports identified from snowballing of full text bibliographies (n = 1)
Reports excluded because:
Wrong patient population (n = 29)
Wrong study design (n = 15)
Wrong comparator (n = 12)
Wrong setting (n = 1)
Full text not obtainable (n = 1)
Included
Studies included in review
(n = 13)
Reports of included studies
(n = 13)

Figure 2. PRISMA flow diagram of study selection. Adapted from PRISMA.[52] PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

1 paper was identified through review of full-text bibliographies of selected papers but since the complete article was not available to reviewers it was excluded from the final selection.[67] Thirteen studies were ultimately selected for this review, as outlined in the provided PRISMA flowchart. Study characteristics pooled from selected studies are summarized in Supplemental Content 1, Tables 1–3, http://links.lww.com/AA/E629. In several studies[40–44,46,68] subgroups were established, as authors sought to explore the

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efficacy of carotid ultrasound under different conditions including variation in carotid parameters,[41–43,68] carotid parameter calculations,[44] respiratory settings[40] and patient clinical state.[46] We analyzed these subgroups independently, as the vast majority included outcomes consistent with our predetermined search strategy (see Supplemental Digital Content 1, Tables 3 and 4, http://links.lww.com/AA/E629). As a result, the total number of patient subgroups analyzed (26) exceeds the number of selected studies (13). Two subgroups of the Roehrig et al[68] study could not be utilized for statistical analysis as the sensitivity and specificity values were not provided. Six different carotid parameters were identified, in descending frequency of use [number of subgroups in parentheses] these were as follows: corrected flow time (FTc) [9],[40,41,44] change in carotid Doppler peak velocity (ΔCDPV) [9],[26,29,41–43,47,68–70] change in carotid artery velocity-time integral ΔCAVTI [4],[42,46] carotid Doppler peak velocity (CDPV) [2],[43,68] carotid Doppler flow (CDF) [1],[68] and change in corrected flow time ΔFTc [1].[45] The method of obtaining carotid Doppler parameters is outlined well in existing literature.[34] However, we provide an illustration of carotid Doppler waveform morphology in Supplemental Digital Content 1, Figure 2, http://links.lww.com/AA/E629.

Five different CO measures were used to identify fluid responders. In descending frequency of use [number of subgroups in parentheses], these were as follows: transthoracic echocardiography (TTE) velocity-time integral (VTI) [8],[42,43,46,47] PiCCO (PULSION Medical Systems AG) [6],[40,69,70] pulmonary artery catheter (PAC) [5],[26,29,68] FloTrac (Edwards Lifesciences) [5],[44,45] and LiDCO (LiDCO Ltd) [2].[41] Six studies (15 subgroups) were conducted on surgical patients,[26,40,41,44,45,68] whereas 7 studies (11 subgroups) were conducted on intensive care patients.[29,42,43,46,47,69,70] Four studies (8 subgroups) were conducted in the OT,[26,40,41,45] and the remaining 9 studies (18 subgroups) were conducted in the ICU.[29,42–44,46,47,68–70]

All patients were mechanically ventilated with documented TV ranging from 6 to 10 mL/kg. Intravenous (IV) fluid administration was the most common method of increasing LV preload to determine fluid responsiveness. Seven studies (12 subgroups) used crystalloid solution,[29,42–44,47,69,70] 4 studies (8 subgroups) used hydroxyethyl starch (HES) solution,[26,40,41,45] and 2 studies (6 subgroups) used the passive leg raise maneuver (PLRM).[46,68] The range of fluid volume administered [number of subgroups/studies in parenthesis] was as follows: 7 mL/kg (11 subgroups/5 studies),[29,40–43] 8 mL/kg (4 subgroups/1 study),[44] 200 mL (2 subgroups/2 studies),[69,70] 250 mL (2 subgroups/2 studies),[45,47] and 6 mL/kg (1 subgroup/1 study).[26] The threshold of fluid responsiveness varied among studies (8 different thresholds in total. The most frequent thresholds used were a ≥15% increase in CO (7 subgroups, 3 studies)[40,43,47] and a ≥15% increase in stroke volume index (SVI) (6 subgroups, 3 studies).[26,29,44] In total, 648 patients underwent 677 fluid challenges, of which 378 (58.3%) were recorded as positive.

Risk of Bias and Quality of Evidence

Risk of bias is summarized in Figure 3. Patient selection incurred risk as all studies failed to outline a recruitment strategy. Index test results may have been unreliable in certain patient cohorts (eg, high-grade carotid stenosis or arrhythmias) many of which were not excluded from several studies.[26,40,42,43,45,47,68–70] In other studies, the independence of index testing and reference standard was unclear,[40,42,47,68–70] and in 1 study the same person performed both measurements,[43] creating bias risk for both measures. This bias was probably overstated in the absence of intentional misconduct, as the ultrasound operator was likely unable to alter carotid blood flow or CO while scanning the patient. Other factors that may have introduced bias include the use of noncalibrated devices to monitor CO[44,45] and an unorthodox manner of determining FR patients: Chen et al[41] allocated patients into FR and non-FR groups based on stroke volume variation (SVV) alone, rather than challenging patients with volume expansion and monitoring the response. No application concerns were held regarding index tests or the reference standard, as both are in keeping with contemporary practice. Furthermore, no application concerns exist regarding patients selected, as all were mechanically ventilated. Deek's funnel plot demonstrated a rejection of the null hypothesis (H0 = slope of 0) (Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/E629); however, some subgroups included may not be considered "independent" given patient overlap, thus interpretation should be done cautiously. The overall quality of evidence was low, with downgrading occurring on account of bias risk and indirectness (Supplemental Digital Content 1, Tables 6 and 7, http://links.lww.com/AA/E629).

Performance of Carotid Ultrasound in Predicting Fluid Responsiveness

Thirteen studies were considered for quantitative analysis, although 2 subgroups[68] were unable to be analyzed as the sensitivity and specificity values were not published. Diagnostic data for each study is summarized in Supplemental Digital Content 1, Table 4, http://links.lww.com/AA/E629. The most reported carotid parameters were ΔCDPV and FTc. Across all 13 studies, carotid parameters varied in accuracy of predicting fluid responsiveness: sensitivity and

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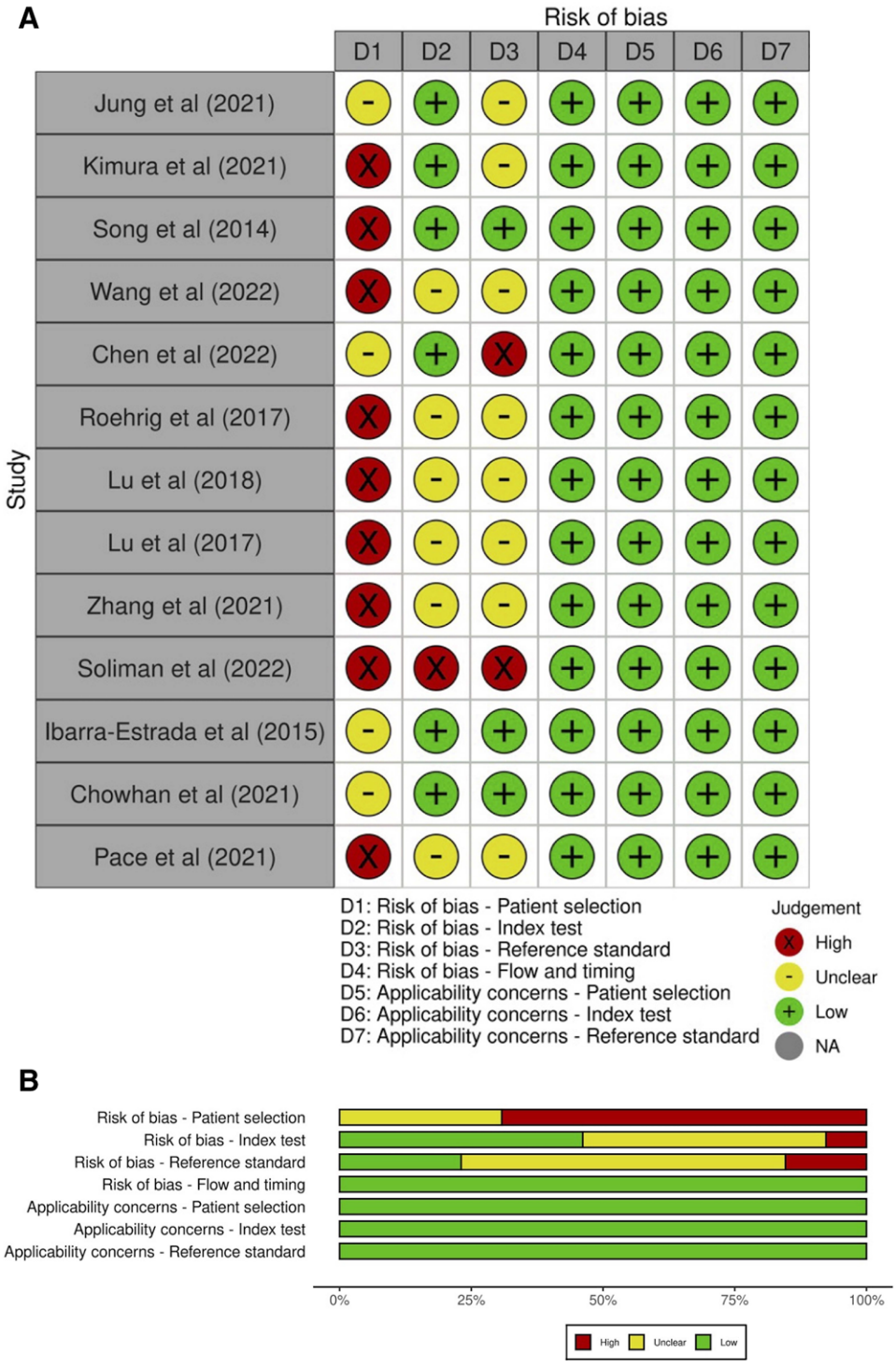

Figure 3. Assessment of bias. A, Assessment of risk of bias as per the QUADAS-2 tool. B, Risk of bias assessment graded by QUADAS-2 domain. QUADAS-2 indicates Quality Assessment of Diagnostic Accuracy Studies-2.

specificity, respectfully, ranged from 0.70 to 0.87 and 0.68 to 0.95 for ΔCDPV,[26,29,41–43,47,68–70] 0.68 to 1.00 and 0.70 to 1.00 for FTc,[40,41,44] and 0.71 to 0.89 and 0.69 to 0.86 for ΔCAVTI.[42,46] A range of sensitivity or specificity values for CDPV, ΔFTc, and CBF were not determinable, owing to their reduced frequency of use or unavailability.

Two carotid parameters proved amenable to meta-analysis: ΔCDPV and FTc. HSROC models (Figure 4) and Forest plots (Figure 5) were constructed and the relevant data is viewable in the Supplemental Digital Content 1, Table 5, http://links.lww.com/AA/E629. Meta-analysis of 9 subgroups that used ΔCDPV as the carotid parameter yielded the following pooled results: sensitivity 0.79 (95% CI, 0.74–0.84) and specificity 0.85 (95% CI, 0.76–0.90). The 95% predictive region of the HSROC suggests that future studies would encounter similar sensitivity results however

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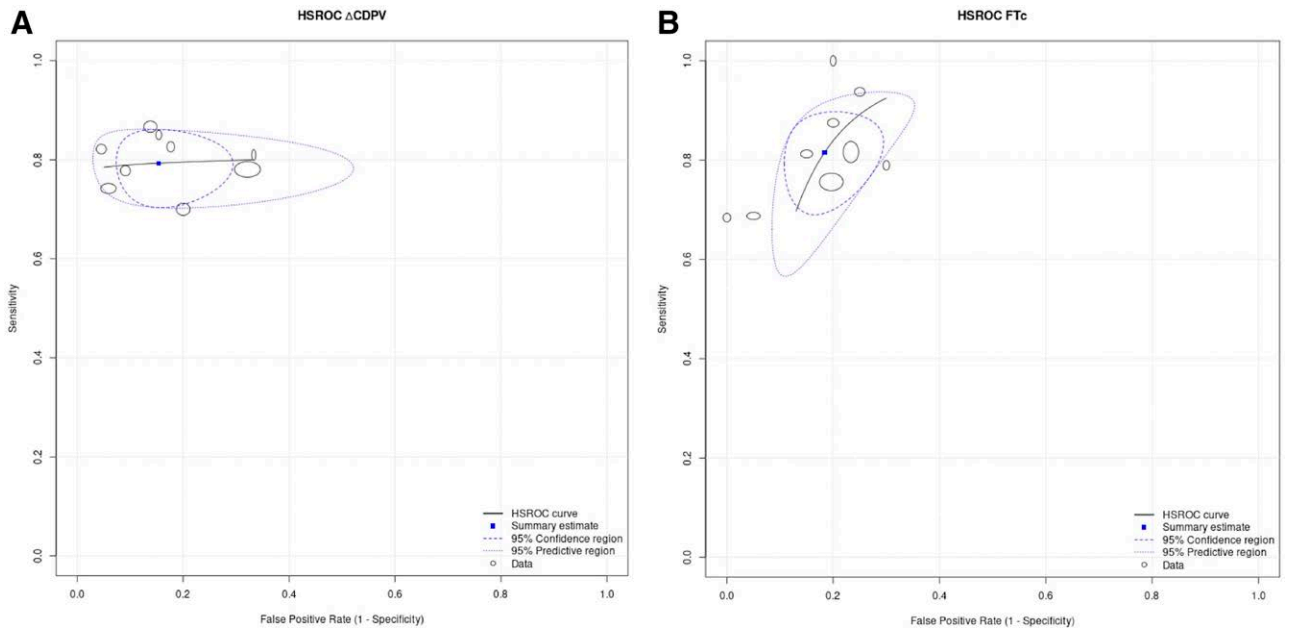

Figure 4. HSROC models of ΔCDPV (A) and FTc (B) subgroups. Size of circle represents weight of study. ΔCDPV indicates carotid Doppler peak velocity; FTc, corrected flow time; HSROC, hierarchical summary receiver operating characteristic.

specificity values may be higher or lower, more likely the latter.

Meta-analysis of 9 subgroups that used FTc as the carotid parameter yielded the following pooled results: sensitivity 0.82 (95% CI, 0.74–0.87) and specificity 0.82 (95% CI, 0.75–0.87). The 95% predictive region of the HSROC suggests that future studies would encounter similar specificity values; however, sensitivity values may be higher or lower with roughly approximate likelihood. A comparison of diagnostic performance between ΔCDPV and FTc using HSROC-derived AUROC values was not possible, due to a dearth of data related to FTc; however, DOR values were comparable (Supplemental Digital Content 1, Table 5, http://links.lww.com/AA/E629).

Heterogeneity

Inspection of the Forest plots for ΔCDPV (Figure 5A) reveals mild-to-moderate heterogeneity, impacting on specificity more so than sensitivity. This is represented in the HSROC model (Figure 4A), whereby the 95% predictive region is skewed to reflect greater heterogeneity in specificity compared with sensitivity. Inspection of the Forest plots and HSROC model for FTc (Figure 5B and Figure 4B, respectively) reveals a similar magnitude of heterogeneity; however, the shape of the HSROC model indicates that there is an even distribution of heterogeneity between sensitivity and specificity. The Spearman's coefficient for ΔCDPV and FTc was calculated to be 0.07 (P = .86) and −0.62 (P = .08), respectively, as such the null hypothesis (no

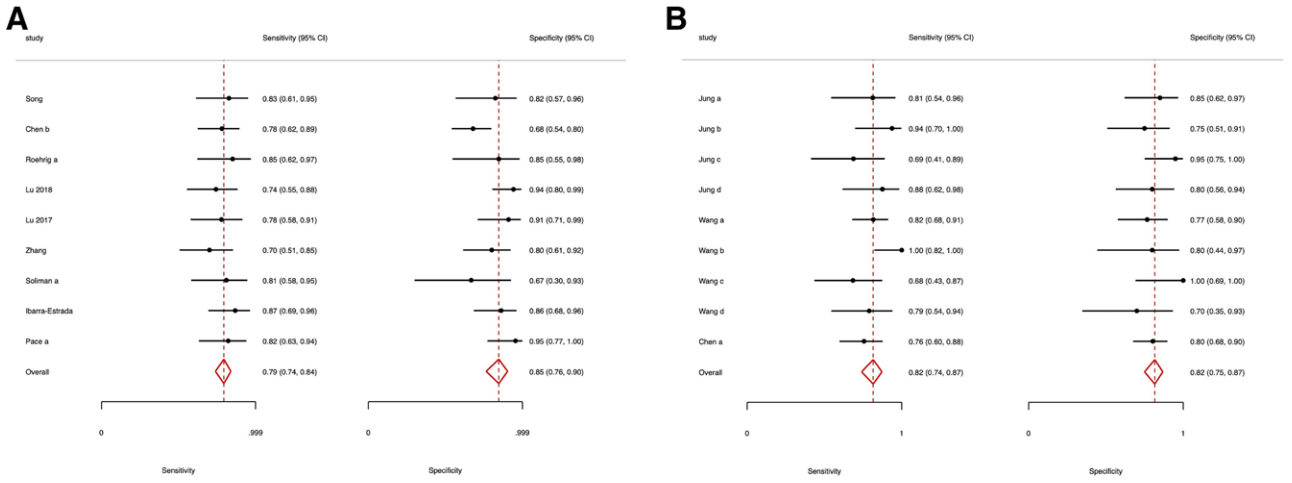

Figure 5. Forest plots of ΔCDPV (A) and FTc (B) subgroups. ΔCDPV indicates carotid Doppler peak velocity; FTc, corrected flow time.

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significant correlation between the 2 variables) is not rejected.

DISCUSSION

In this meta-analysis of 13 trials and 648 patients, we found that use of carotid ultrasound, specifically ΔCDPV has at least moderate accuracy[71] in predicting fluid responsiveness in mechanically ventilated adults. Meta-analysis of ΔCDPV yielded a sensitivity of 0.79 and specificity of 0.85 based on low-quality evidence. Meta-analysis of FTc yielded similar results and similar quality of evidence. AUROC values for ΔCDPV and FTc could not be directly compared; however, DOR values were comparable confirming similar predictive accuracy. Heterogeneity was present for ΔCDPV and FTc and likely reflected differences in study design. Other carotid parameters assessed included ΔCAVTI, ΔFTc, and CDPV; however, these tests were unable to undergo meta-analysis and were variable in their diagnostic accuracy. Bias was present in all included studies, albeit variable in severity, and meta-regression was unable to be performed owing to a dearth of data.

Our analysis updates the 2018 meta-analysis performed by Yao et al,[39] adding 6 additional studies[41–43,47,68,69] and 335 patients. The accuracy of ΔCDPV in our analysis underperformed in comparison, likely due to different studies included in each analysis. Three studies not analyzed by Yao et al[39] on account of being published later found slightly worse diagnostic accuracy of ΔCDPV.[41,43,47] Another study,[68] identified but ultimately excluded from analysis by Yao et al,[39] also yielded a lower diagnostic accuracy and was excluded on the grounds of bias from the PLRM. In our opinion, the PLRM has been a well-validated method of achieving volume expansion via auto-transfusion,[72] as such we included PLRM studies in our analysis. Use of PLRM probably affects generalizability more than bias, as it is impractical to perform in most sterile surgical settings. Furthermore, we did not include 1 study[67] analyzed by Yao et al[39] as we were unable to obtain a full-text version. This likely contributed further to the observed difference in diagnostic accuracy of ΔCDPV as the reported accuracy was very high.

Our findings are similar to another systematic review and meta-analysis[35] performed in 2022. While diagnostic accuracy was again slightly worse in our analysis, the results may be subject to confounding owing to the inclusion of 2 studies of spontaneously breathing patients.[30,73] This effect has been observed in a prior narrative review[34] that examined 23 studies using carotid parameters to predict fluid responsiveness, documenting a median AUROC of 0.82 for ventilated patients and 0.71 for spontaneously breathing patients. This could be explained by the heart-lung interactions that underlie dynamic methods of assessing fluid responsiveness,[25] an effect illustrated by the interdependence of TV[74,75] and lung compliance[76] on diagnostic performance. Carotid ultrasound may similarly require cyclical ventricular loading conditions caused by mechanical ventilation to deliver performative results. In summary, our results are consistent with prior analysis and although they represent a reduction in diagnostic accuracy, the difference is accounted for by study selection.

Our analysis suggests that ΔCDPV, and to a lesser extent FTc, may be useful clinical adjuncts in predicting fluid responsiveness of mechanically ventilated patients. However, we found considerable variation in the methodology used in the included studies, as such we advocate for a considered application of this technologically. Notably, the threshold used for fluid responsiveness varied. One 2022 study[41] utilized ΔSVV as an end point, itself often used as a predictor of fluid responsiveness, thus FR prevalence in this study should be interpreted with caution. Furthermore, some studies described a wide diagnostic "gray zone,"[41,44] an issue not isolated to carotid ultrasound.[17] CO output was also measured with different modalities, several studies utilized a PAC[26,29,68] while others used TTE-derived VTI.[42,43,46,47,77] Despite evidence of PiCCO[77–84] and LiDCO[80,85–87] performing reliably, both suffer from drift and require constant recalibration.[84,88] Drift mitigation was not addressed in 4 studies utilizing this technology[40,41,69,70] although one[40] reduced bias by excluding patients requiring vasoactive drugs. The uncalibrated FloTrac device is prone to CO discordance when vasomotor tone changes.[89–95] It was used in 2 studies,[44,45] 1 of which[45] did not exclude patients on vasopressor supports. A more consistent use of gold-standard CO modalities in future studies would minimize bias and confounding.

The patient condition may also have introduced variability into our results. Of the 6 studies that included OT patients,[26,40,41,44,45,68] all but two[26,40] failed to specify whether cases were elective or emergency. Among ICU patients who had not undergone surgery, the most common clinical state was shock[29,43,46,47,69,70] due to sepsis. Several studies failed to exclude patients with conditions affecting carotid assessment including severe carotid stenosis,[40,45,47,68–70] arrhythmias[42,43,68–70] and AV disease.[26,40,43,68–70] Generally, the OT cohorts excluded patients with multiple comorbidities more than the ICU cohorts; however, most studies excluded HF patients[26,29,40,43–45,47,69,70] likely due to fluid challenge contraindication. Male patients were overrepresented in every study. TV varied between studies and in several[43,46,69] a value was not specified. Variable TV likely affected all parameters except FTc which is

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comparably accurate across both low and high TV groups.[44] Finally, although only 2 studies chose the PLRM,[46,68] fluid bolus volumes of the remaining studies were not uniform. To summarize, application of carotid ultrasound should consider the patient's sex, clinical setting, comorbidities, clinical state including vasopressor requirements, and mode of volume expansion.

Our study has limitations. As previously noted, our analysis is primarily limited by study design heterogeneity, intrastudy bias, and low quality of evidence.

Exclusion of patients with specific comorbidities precludes generalization and a lack of clear diagnostic cutoffs limits translation to practice. Our dataset may have also been impacted by the exclusion of articles in languages other than English from searches, and finally, the effect of study covariates on diagnostic accuracy remains to be examined.

In conclusion, our updated systematic review and meta-analysis included several papers not previously reviewed and continues to support the accuracy of carotid ultrasound to predict fluid responsiveness in mechanically ventilated adult patients. Specifically, ΔCDPV may be an accurate parameter although cutoff values are yet to be defined. To overcome challenges with interpretation and generalizability, further high-quality studies with consensus are needed, to further validate this widely available and noninvasive technology.

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DISCLOSURES

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